REMARKS

I. Status of the claims and Support for Amendment

Claims 1, 2, and 4-22 are currently pending.

II. Rejection under 35 U.S.C. § 103

A. Claims 1, 4, 5, and 8-22 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Magruder (USPN 5,037,420) in view of Mitchell (USPN 5,474,980). The Examiner specifically alleges that:

> [i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have formulated the composition disclosed in Magruder in the biocompatible oil/aluminum monostearate vehicles taught by Mitchell because Mitchell teaches that the oil/monostearate vehicles are useful for prolonged parenteral release of somatotropin *in vivo*."

Applicant respectfully traverses.

MPEP chapter 2100 sets forth the standard which must be satisfied in combining two references. It states, in pertinent part:

> "[t]here are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obviousness was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

MPEP §2143.01.

MPEP 2143.01 further states that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)." Emphasis in the original. Applicant unequivocally asserts that the instant rejection does not satisfy the standards set out above. The cited references provide no motivation to combine them so as to

provide the instantly claimed invention. The Examiner states that it would have been obvious to combine the teachings of Magruder and Mitchell because "Mitchell teaches that the oil/monostearate vehicles are useful for prolonged parenteral release of somatotropin *in vivo*." However, this statement merely recommends the benefits of using the oil/monostearate vehicles described in Mitchell. The statement provides no evidence of a teaching or motivation for combining the teachings of Mitchell with those of Magruder.

Furthermore, there is no teaching or suggestion in the combination of the cited references that the benefits envisioned by the compositions described in Magruder, as comprising a surfactant, would be realized in a non-aqueous environment as described in Mitchell. Similarly, Mitchell provides no teaching or suggestion of the benefit of modifying the compositions described in Magruder for use in a non-aqueous environment. On the contrary, taken as a whole, Applicant contends that Magruder is properly characterized as "teaching away" from combination with Mitchell.

Referring to pharmaceutical carriers disclosed therein, Magruder recites that they comprise "beneficial agent **20**, pharmaceutically acceptable viscosity modulating vehicle **23**, a buffer **22**, or a buffer solution **22** and a surfactant **24**." Magruder, col. 14, ll. 38 and 39 (emphasis in original). Magruder further states that in a "preferred embodiment the buffer and solution thereof is used in combination with the pharmaceutically and pharmacologically acceptable **aqueous miscible** fluids." Magruder, col. 15, ll. 10-13 (emphasis added). There is no mention in Magruder of any non-aqueous buffers, nor of the benefits of such. From this, one of ordinary skill in the art would conclude that the Magruder teaches that any compositions described therein as comprising a surfactant only exhibit their beneficial characteristics in the presence of an aqueous buffer.

Thus, Magruder does not teach or suggest any non-aqueous surfactant containing and does not teach or suggest the desirability of compositions comprising surfactants in a "substantially non-

aqueous hydrophobic carrier [which] composition is fluidly injectable at 25 °C." Further Mitchell does not teach or suggest any motivation for providing a composition comprising a non-ionic surfactant and a non-reducing carbohydrate or oxo-acid salt.

The *Al-Site* holding, *supra*, provides that in the absence of a motivation to combine the cited references, a rejection under 35 U.S.C. §103(a) is improper. In view of the arguments presented above, Applicant asserts that the holding in *Al-Site* is applicable to the instant rejection. Accordingly, Applicant believes that the instant rejection has been overcome and may properly be withdrawn.

B. Claim 2 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Magruder in view of Mitchell, as applied to claims 1, 4, 5, and 8-22, above, and further in view of Scarborough (USPN 6,162,258). Scarborough is cited as allegedly teaching "a polyoxyethylene sorbitan fatty acid ester and a polyoxyethylene fatty acid ester mixed with a growth hormone such as somatotropin...." Applicant respectfully traverses.

In view of the arguments set out in part "A.," Applicant believes that it has been clearly demonstrated that the combination of Magruder and Mitchell does not render the instantly claimed invention obvious. Applicant further contends that Scarborough adds nothing to the combination of Magruder and Mitchell to alter this result. In fact, Scarborough does <u>not</u> describe somatotropin compositions at all; rather, Scarborough describes a method for preserving and rehydrating monolithic bone, for use as a bone graft. The surfactants cited by Examiner are included only as part of an extensive laundry list (~80 compounds) of "mechanical strength-conserving agents" which can be used to treat the prepared bone fragment prior to lyophilization (*see*, col. 4, ll. 45 through col. 5, ll.31). Therefore, Scarborough provides no teaching or

suggestion that such non-ionic surfactants might be useful to enhance the bioavailability of any substance, let alone of somatotropin.

Similarly, somatotropin is only included in the Scarborough specification as part of a long laundry list of compounds that may, *optionally*, be added to the solution used to rehydrate the bone (*see,* col. 6, ll. 30-49). Thus, Scarborough cannot be accurately viewed as teaching or suggesting that a composition comprising a surfactant and somatotropin is desirable or advantageous. In fact, Scarborough does not even teach a composition comprising somatotropin and a surfactant. Rather, Scarborough lists both compounds as part long lists of possible agents that might, separately, be useful as components of separate solutions the surfactant for strengthening the bone and the somatotropin as an *optional* component of the rehydrating solution (meaning that somatotropin is not a necessary component). Given that Scarborough provides no motivation to specifically combine the somatotropin and surfactant and further given the astronomical number of possible combinations of the 80+ strengthening agents and 40+ optional wetting agents or medically/surgically useful substances, one of ordinary skill in the art would not consider it obvious to specifically combine the somatotropins and surfactants listed in Scarborough.

Moreover, even if the surfactant and the somatotropin were selected from among the long lists disclosed, Scarborough teaches that they are suitable for addition to the monolithic bone, not to be injected into an animal. Consequently, the composition taught by Scarborough comprises the monolithic bone, which is certainly not "fluidly injectable" (as Scarborough teaches, the monolithic bone must be surgically implanted).

In view of these facts, Applicant contends that there is nothing in the combination of Magruder, Mitchell, and Scarborough which teaches or suggests combining the references so as

to obtain the instantly claimed invention. Consequently, Applicant asserts that the rejection of the claims as being unpatentable over the combination of these references has been overcome and may properly be withdrawn.

C. Claims 6 and 7 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Magruder in view of Mitchell, as applied to claims 1, 4, 5, and 8-22, and further in view of Hamilton (USPN 4,816,568). Hamilton is cited as allegedly teaching polyols present in amounts from about 2.5% to about 99%, by weight of the formulation. The examiner alleged that:

> [i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have added the polyol stabilizer of Hamilton to the composition disclosed by Magruder in view of Mitchell in order to enhance the bioavailability of the somatotropin in the composition, because Hamilton teaches that growth hormones may be admixed with various stabilizers to provide for the preservation of the soluble bioactivity of the growth hormone, see abstract.

Applicant respectfully traverses.

In view of the arguments set out in part "A.," Applicant believes that it has been clearly demonstrated that the combination of Magruder and Mitchell does not render the instantly claimed invention obvious. Applicant further contends that Hamilton adds nothing to the combination of Magruder and Mitchell to alter this result.

Hamilton describes only mixtures of growth hormones and a "stabilizer" selected from a polyols, amino acids, a polymer of an amino acid, or derivatives of choline (*see*, col. 5, ll. 40-53). Hamilton teaches that the somatotropin compositions can be in a "liquid form or solution which is administered by subcutaneous injection," alternatively the "stabilized growth hormone formulation [can be] compressed into a tablet or pellet form . . ." (*see*, Hamilton col. 5, ll. 56-65). Hamilton further recites that:

> [w]hen an injectable form of the stabilized growth promoting formulation is desired, the stabilizer is first dispersed in an aqueous solution which can be stirred or shakened [sic] to bring about a more rapid solubilization of the stabilizer.

> After the aqueous solution of the stabilizer has been formed, the growth hormone is added.

(Hamilton, col. 4, line 67 through col. 5, line 5, emphasis added). Thus, Hamilton provides for either an aqueous solution of somatotropin or a solid composition of somatotropin. Hamilton provides no teaching or suggestion that a composition "wherein the somatotropin and a bioavailability enhancing constituent are suspended in a substantially *non-aqueous* hydrophobic carrier" would be advantageous.

In contrast, it is an important objective of the instant invention to protect the somatotropin from water, which reduces its stability. The instantly claimed invention accomplishes this objective by combining the somatotropin with one or more bioavailability enhancing constituents in a non-aqueous environment and maintaining this environment through injection by keeping the somatotropin suspended in the non-aqueous vehicle.

In view of the foregoing, Applicant contends that there is nothing in the combination of Magruder, Mitchell, and Hamilton which suggests any advantage for combining the teachings of those references so as to achieve the instantly claimed invention. On the contrary, the cited references "teach away" from the instantly claimed invention by teaching, in the alternative, aqueous solutions of somatotropin or somatotropin compositions which are solid. For these reasons, Applicant contends that the rejection of the instantly pending claims as being unpatentable over the combination of Magruder, Mitchell, and Hamilton has been overcome and may properly be withdrawn.

III. Summary

In view of the above Remarks, Applicant believes that all rejections of the claims have been overcome and that the instant case is in condition for immediate allowance. Consequently, Applicant

respectfully requests favorable reconsideration of the Application and issuance of a "Notice of Allowance" therefor.

The Examiner is invited to contact the undersigned patent agent at (713) 787-1589 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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